REMARKS

The title of the published application (US2006-0135448) contains a spelling error. Microcirculatory is incorrectly spelled as Microcircula**troy**. However, the term is correctly spelled in the application as filed and had not been amended. Thus, an amendment to the title has not been made. Applicants respectfully request clarification.

Claims 11 and 20 have been amended, as suggest by the Examiner. The extra "of" in claim 11 and the extra period in claim 20 have been deleted. No new matter has been added.

Rejections under 35 USC §102

Claims 1 - 6 and 20 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Bissett et al. (WO 95/27485).

Bissett et al. discloses a composition comprising a compound to reduce free radical damage to the skin. Numerous compounds are disclosed, one of which is 1,2-dimethyl-3 hydroxy-pyrid-4-one (i.e., deferiprone). The compounds may be delivered orally, topically or by injection. See pages 6, 7 and 8.

On page 3 of the Office Action, the Examiner states:

> "Bissett et al. discloses topically administering the hydroxypyridonone deferiprone. Therefore, the treatment of skin microcirculatory disorders and the specific disorders listed in claim 20 must inherently be met as both the cited prior art and the instant claims recite topically administering the hydroxypyridonone deferiprone."

Applicants, respectfully disagree with this assertion. Bissett teaches that free radicals in mammalian cells may arise from environmental sources such as smoke, pollution and radiation. (See page 1, lines12-14). In addition, Bissett teaches that free radicals play a role in HIV. See, for example, page 1 at lines 23-25. Nowhere does Bissett teach or suggest the treatment of skin microcirculatory disorders (SMD). Bissett is particularly silent regarding treatment of purpura, rosacea capillaritis, rosacea, cutaneous vasculitis, itching purpura, purpura annularis telangiectodes, contact allergy skin capillaritis, traumatic skin hemorrhage or actinic purpura.

A skilled worker would simply not expect that a person being treated with a compound to reduce free radical damage from, for example, smoke, pollution, radiation or HIV would also necessarily have a microcirculatory skin disorder. The mere possibility that a person being treated for smoke damage, for example, may also have a microcirculatory skin disorder is not sufficient to establish inherency. In other words, the person being treated with deferiprone to reduce free radical damage from smoke, pollution, radiation or HIV must always also have a microcirculatory skin disorder in order to establish inherency.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

Thus, based upon the above remarks, it is respectfully requested that the rejection under 35 USC 102 be withdrawn.

Rejections under 35 USC §103

Claims 1 - 6, 11 - 13, 16, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bissett et al. (WO 95/24785) in view of Perricone (US 2002/0013361) and Claims 1 - 6, 11 - 14, 16, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bissett et al. and Perricone further in view of the purpura entry from DermNet NZ.

Bissett et al. (WO 95/24785) discloses numerous compounds for the treatment of free-radical damage. One such compound may be 1,2-dimethyl-3hydroxy-pyrid-4-one (i.e., deferiprone). Bissett teaches that free radicals in mammalian cells may arise from environmental sources such as smoke, pollution and radiation. (See page 1, lines12-14). In addition, Bissett teaches that free radicals play a role in HIV. See page 1, lines 23-25. The compounds may be delivered orally, topically or by injection. See pages 6, 7 and 8. The active ingredients are iron chelating compounds that reduce the level of free radicals in mammalian cells (p 1, line 8 - 10).

Perricone (US 2002/0013361) discloses that lipoic acid is useful to treat rosacea. Perricone does not teach or suggest that lipoic acid is an iron chelator. Furthermore, Perricone does not teach or suggest a hydroxypyridonone compound of formulae (I-III).

The web pages from DermNet NZ concern several of the diseases claimed in the method of the present invention. The reference relates to the etiopathological causes of select skin microcirculatory disorders (SMD). In particular, DermNet NZ teaches that the different types of purpura are caused by the destruction of platelets, drugs, infections, certain diseases, damage to small blood vessels, increase of the intraluminar pressure, deficient vascular support or disseminated intravascular coagulation. DermNet NZ also teaches that vasculitis is caused by direct injury to the vessels wall by bacteria or viruses, by activation of antibodies or by the activation of complement. In addition, DermNet NZ teaches that capillaritis arises as a reaction

to a medication, to a reaction to some drugs; or a reaction to food additive or viral infections.

There is no indication that any of these pathologies are generated by free radical damage or a problem arising from the presence of an excess of iron. Accordingly, a skilled worker having knowledge of the etiopathology discussed above, would not try to treat said diseases with a compound of formula I-III (e.g., deferiprone) which is known to be an iron chelator. Furthermore, the DermNet NZ reference suggests treatments for said pathologies. For Purpura the reference teaches that the underlying cause of purpura should be identified and treated accordingly. For vasculitis the reference teaches a skilled worker to treat the underlying infection; discontinue medications such as corticosteroids, colchicine; dapsone or hydroxychloroquine. For capillaritis the reference suggests the removal of the possible cause, such as a food additive or a medication and recommends topical steroids or graduated compression elastic hose. Nowhere in the DermNet NZ reference is there any suggestion that the application of an iron chelator (e.g., deferiprone) would be successful in the treatment of SMD's. A skilled worker would not expect that a compound of formula I-III, such as deferiprone, would be successful in the treatment of SMD's such as purpura, vasculitis, capillaritis and similar pathologies.

Bissett teaches treatment of free radical damage from e.g. smoke or radiation and not treatment of SMD's. Perricone discloses that lipoic acid is useful to treat rosacea. Perricone does not teach or suggest that lipoic acid is an iron chelator. Furthermore, Perricone does not teach or suggest a hydroxypyridonone compound of formulae (I-III). Consequently, a skilled worker would have no motivation to combine Bissett et al or Perricone in order to use deferiprone in the treatment of SMD's. There is no correlation between lipoic acid and deferiprone, an iron chelator. Likewise, a skilled artisan would find no suggestion in DermNet NZ for the use of an iron chelator in the treatment of rosacea, vasculitis, purpura and capillaritis. On the contrary, a skilled worker would have thought that deferiprone was not able to treat said diseases, as it does not interfere in any of the etiopathological causes thereof.

Claims 1 - 6, 11 - 14, 16, 19 and 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ghisalberti et al. (WO 01/17497) in view of Murad (US 6,630,163).

Neither Ghisalberti nor Murrad provide any suggestion or teaching that would lead a skilled worker to try a compound of formula I-III (i.e, iron chelators) for the treatment of pathologies whose etiopathologies are in no way linked to free radical damage or to the presence of an excess of iron.

Ghisalberti ('497) describes a cosmetic and/or dermatological composition and a method for the treatment and/or prevention of hyperpigmented skin. Ghisalberti's composition may comprise 3-hydroxypyr(id)one derivatives.

Ghisalberti is entirely directed to the treatment of pathologies resulting from an impairment of the activity of melanocytes, such as the increased production of melanin resulting in hyperpigmentation. As noted above in the DermNet NZ reference, which discusses the pathologies of certain SMD's, the claimed pathologies are not in any way related to the production of melanin resulting in hyperpigmentation.

On page 3, lines 10-11 of Ghisalberti states: "the formation of pigmentary spots may result from the combination of blood extravasation around the injection site". However, blood fluid leakage at an injection site is not the result of a pathology caused by a skin microcirculatory disorder. Injection site blood is a side effect of a punctured blood vessel. Furthermore, the hemoglobin in injection site blood leakage is promptly bound to dermal and connective proteins forming hemosiderin deposits, which in turn may stimulate the activity of the surrounding melanocytes. A skilled worker would recognize that spots that are hemosiderinic in nature do not arise from microcirculatory disorders but rather hemosiderin spots are the result of increased production of melanin.

Ghisalberti is silent regarding the treatment of skin microcirculatory disorders.

Ghisalberti is particularly silent regarding treatment of purpura, rosacea capillaritis, rosacea, cutaneous vasculitis, itching purpura, purpura annularis telangiectodes, contact allergy skin capillaritis, traumatic skin hemorrhage or actinic purpura.

Thus, Ghisalberti only deals with the treatment of hyperpigmented skin which results from excess of melanin and/or by hemosiderin deposits, thus making the skin turn to a brown color. Spots that are hemosiderinic in nature do not arise from microcirculatory bleeding. Pathologies caused by skin microcirculatory disorders are not similar to the hyperpigmentation disorders disclosed in Ghisalberti and as the DermNet NZ reference discussed above makes clear, the etipathologies of SMD's are not the result of hyperpigmentation. Thus, a skilled worker would not look towards a hyperpigmentation treatment to treat SMD's.

Murad et al. (US 6,630,163) teaches the use of fruit extracts for neutralizing free radicals. Murad is silent regarding iron chelators. At col. 7, line 65 to Col. 8, line 12 Murad lists numerous etiologically different dermatological disorders that may be treated with fruit extracts.

> "The term "dermatological conditions," as used herein, means conditions present anywhere on the skin caused by aging or extrinsic factors such as sunlight, radiations, air pollution, wind, cold, dampness, heat, chemicals, smoke, and smoking. Dermatological conditions include, but are not limited to, dry skin; dandruff; warts; acne; keratosis; psoriasis; eczema; pruritus; age spots; reduced skin moisture; spider veins; senile purpura; lentigines; melasmas; deepening of skin lines; blotches; wrinkles; blemished skin; nodules; atrophy; rosacea; impetigo; precancerous lesions; elastotic changes characterized by leathery, course, rough, dry and yellowish skin; telangiecatic skin; hyperpigmented skin; hyperkeratotic skin; nail infections; inflammatory dermatoses; and damage to hair including, but not limited to, hair breakage, weathering damage, and thinning of hair. "

Thus, the reference broadly teaches a method for treating almost any dermatological disorder. Included in the list are some microcirculatory skin disorders such as senile purpura and rosacea. The list also includes hyperpigmented skin. Whatever its merits, Murad does not teach that an agent useful for treating hyperpigmented skin is useful for treating microcirculatory skin disorders, and vice versa. Its disclosure is limited to fruit extracts. Fruit extracts are not known to be iron chelators. There is no rationale for extrapolating

Murad's teaching to the agents recited in the claims, nor is there any basis in fact for doing so.

Furthermore, according to '163 the fruit extracts can be used to treat any dermatological disorder due to the anti- free radical properties of the extracts. Thus, a variety of pathologies or very different etiology can allegedly be "treated". The '163 patent makes incredible claims regarding its antioxidant fruit extracts, but a skilled worker would recognize that one agent can not, credibly, be used to treat all the pathologies listed in US 6,630,163.

In other words, contrary to the Examiner allegations, US '163, even in the best case, does not teach a skilled worker that any particular compound, which is normally used to treat hyperpigmentation, can also be used for the treatment of microcirculatory skin disorders such as rosacea and purpura. A skilled worker would recognize that the mechanisms of action for hyperpigmentation are very different from the mechanisms of action for SMD's.

Thus, in view of the above, it is respectfully requested that the rejections under 35 USC §103 be withdrawn.

Respectfully submitted,

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